THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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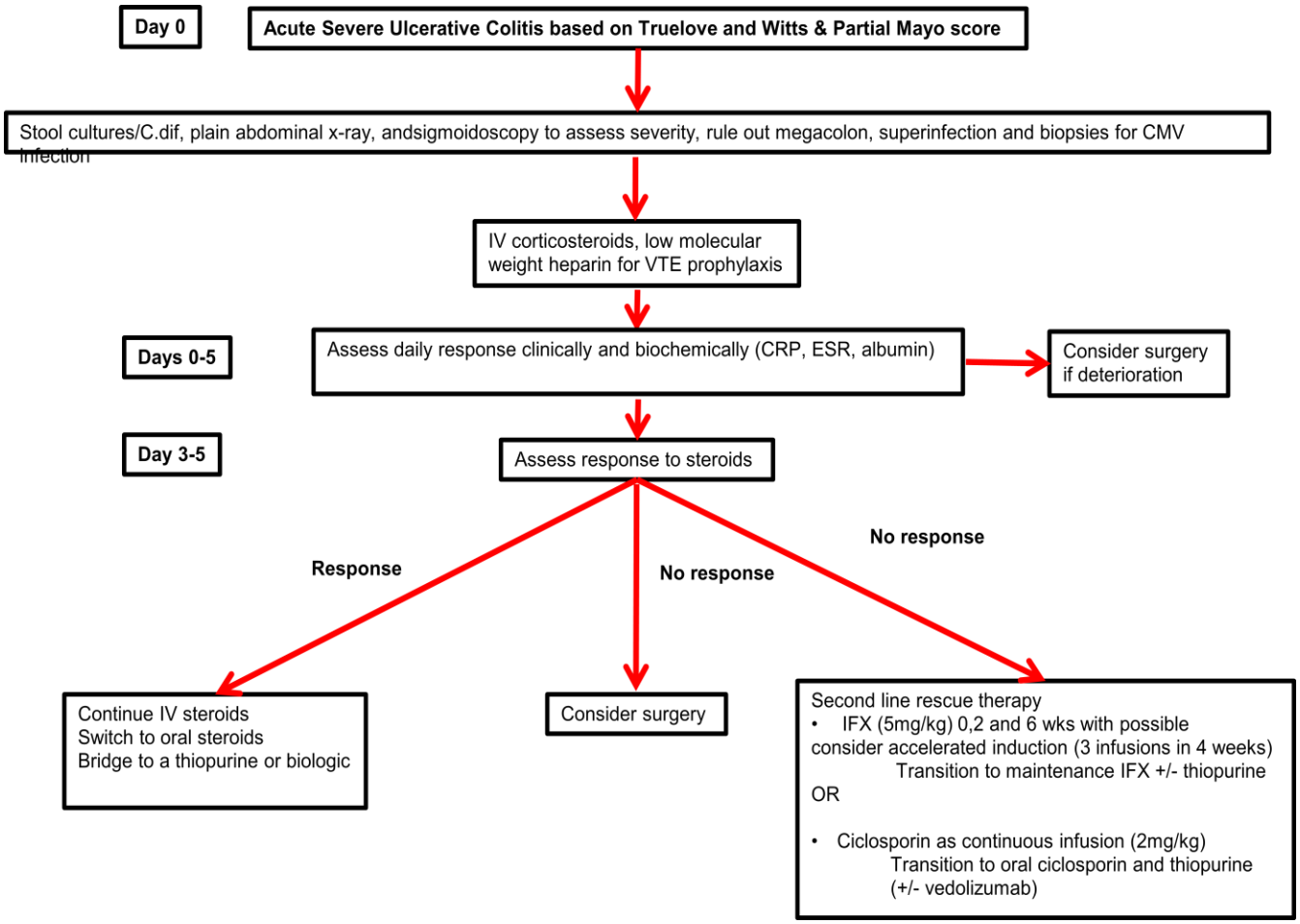
Supplemental Information on Acute Severe Ulcerative Colitis (ASUC)

The main complications of ASUC is fulminant colitis, leading to emergency colectomy.[1] Patients with ASUC should be admitted to hospital due to high risk for colectomy in the short term.[2] In the longer term colectomy is required in approximately 70% of patients with UC within 5 years after initial hospitalization.[3,4].Patients should have stool cultures and C. difficile infection should be excluded as it higher in patients with colitis and is associated with a higher mortality and colectomy rates.[5,6] Patients should have an early endoscopic evaluation for disease severity and biopsies taken for cytomegalovirus (CMV).[7] In addition, CMV infection should be considered prior to escalation of immunosuppressive therapy to minimize the risk of precipitating opportunistic CMV colitis.[8] Venous thromboembolism (VTE) is a potentially fatal complication of IBD during flares. The risk of VTE is three times higher in IBD patient than the general population and this risk increases during a flare.[9] Patients should receive subcutaneous low molecular weight heparin or fondaparinux to reduce risk of VTE. Preventative VTE prophylaxis does not appear to increase the risk of excessive gastrointestinal bleeding in IBD flares and is recommended for all patients with ASUC.[10]

A general treatment approach algorithm to ASUC is presented in the figure below. Of the patients with ASUC who are treated with intravenous (IV) corticosteroids approximately 65 % will respond.[11] Patients who do not respond to IV corticosteroids are considered steroid-refractory and require rescue medical therapy or surgery. The Oxford index is a useful tool to predict those who are high risk for surgery and require rescue therapy.[12] Risk factors that increase the risk of colectomy in ASUC include young age at diagnosis, smoking status, CRP, ESR, fecal calprotectin, and genetic

factors.[13–17] The choice of rescue therapy at present is between infliximab and ciclosporin. There are differences in half-life between infliximab and ciclosporin which may account for differences in efficacy. The efficacy of ciclosporin versus infliximab has been evaluated for ASUC and the results appear comparable although nonrandomized trials suggest infliximab may be associated with lower risk of colectomy.[18] Many centers appear to favor infliximab in ASUC but the choice of drug depends on previous IM failure (anti-TNF appears superior in these patients) and institutional preference. An accelerated infliximab dosing schedule (i.e. induction over 4 weeks rather than 6 weeks) may reduce early colectomy rates in patients with ASUC but does not appear to impact long term risk of colectomy.[19] The important question of accelerated induction of inflixmab in ASUC requires further prospective studies.

Operative management for ASUC should ideally be performed in a semi-elective rather than emergency setting, as this is associated with a lower mortality.[20] In general this surgery involves a two staged technique with proctocolectomy and ileostomy and then if favorable features an ileal pouch-anal anastomosis can be considered. The effect of immunosuppresions on emergency surgery has not shown to be significant in retrospective analyses.[21]


Day 0
Acute Severe Ulcerative Colitis based on Truelove and Witts & Partial Mayo score
Stool cultures/C.dif, plain abdominal x-ray, andsigmoidoscopy to assess severity, rule out megacolon, superinfection and biopsies for CMV infection
IV corticosteroids, low molecular weight heparin for VTE prophylaxis
Days 0-5
Assess daily response clinically and biochemically (CRP, ESR, albumin)
Consider surgery if deterioration
Day 3-5
Assess response to steroids
Response
No response
No response
Continue IV steroids
Switch to oral steroids
Bridge to a thiopurine or biologic
Consider surgery
Second line rescue therapy
• IFX (5mg/kg) 0,2 and 6 wks with possible consider accelerated induction (3 infusions in 4 weeks)
Transition to maintenance IFX +/- thiopurine
OR
• Ciclosporin as continuous infusion (2mg/kg)
Transition to oral ciclosporin and thiopurine (+/- vedolizumab)

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Supplementary Table 1. Extraintestinal Manifestations of Ulcerative Colitis[1,2,3] Most EIMs occur when UC is active. However, ankylosing spondylitis and uveitis are less likely to correlate with luminal disease activity and can follow an independent clinical course.[2,4]

Skin: erythema nodosum, pyoderma gangrenosum, psoriasis, Sweet's syndrome
Joints: peripheral arthritis (Type 1 – pauciarticular, mirrors active IBD; Type 2 – polyarticular, independent of IBD activity), ankylosing spondylitis
Eyes: uveitis, episcleritis
Mouth: aphthous stomatitis
Liver: primary sclerosing cholangitis, autoimmune hepatitis
Lungs: bronchiectasis, cryptogenic organizing pneumonia

Supplemental Table 2. Commonly Used Ulcerative Colitis Clinical Disease Activity Indices

2A. Mayo Score[5]

	Score
Stool Frequency Normal for patient 1-2 more than normal 3-4 more than normal 5 or more stools than normal	 0 1 2 3
Rectal Bleeding No blood Streaks of blood in stool less than half of the time Obvious blood in stool most of the time Blood alone passed	 0 1 2 3
Endoscopy Findings Normal or inactive disease Mild (erythema, decreased vascular pattern, mild friability) Moderate (marked erythema, absent vascular pattern, friability, erosions) Severe (spontaneous bleeding, ulceration)	 0 1 2 3
Physician's Global Assessment *(includes patient symptoms including abdominal discomfort and sense of well-being as well as performance status and physical exam)* Normal Mild disease	 0 1

Moderate disease Severe disease	2 3
	Total Score: 0-12

2B. Lichtiger Score[6]

	Score
Diarrhea (number of daily stools) 0-2 3-4 5-6 7-9 10 or more	 0 1 2 3 4
Nocturnal Diarrhea No Yes	 0 1
Visible Blood in Stool (% of movements) 0 < 50 ≥ 50 100	 0 1 2 3
Fecal Incontinence No Yes	 0 1
Abdominal Pain or Cramping None Mild Moderate Severe	 0 1 2 3
General Well-Being Perfect Very Good Good Average Poor Terrible	 0 1 2 3 4 5
Abdominal Tenderness	 0

None Mild and Localized Mild to Moderate and Diffuse Severe or Rebound	1 2 3
Need for Antidiarrheal Drugs No Yes	 0 1

The maximal score is 21. A score of less than 10 on two consecutive days are considered a clinical response.

2C. Simple Clinical Colitis Activity Index [7]

	Score
Bowel Frequency (during day) 1-3 4-6 7-9 >9	 0 1 2 3
Bowel Frequency (during night) 0 1-3 4-6	 0 1 2
Urgency of Defecation Hurry Immediately Incontinence	 1 2 3
Blood in Stool None Trace Occasionally frank Usually frank	 0 1 2 3
General Well Being Very Well Slightly Below Par Poor Very Poor Terrible	 0 1 2 3 4
Extracolonic Features	1 per manifestation

Supplemental Table 3. Commonly Used Ulcerative Colitis Endoscopic Disease Activity Indices in Ulcerative Colitis

3A. Partial Mayo Score

Endoscopy Findings	
Normal or inactive disease	0
Mild (erythema, decreased vascular pattern, mild friability)	1
Moderate (marked erythema, absent vascular pattern, friability, erosions)	2
Severe (spontaneous bleeding, ulceration)	3

3B. Ulcerative Colitis Endoscopic Index of Severity (UCEIS)[8]

Descriptor (score most severe lesion)	**Finding (Score)**	**Definition**
Vascular pattern	Normal (1)	Normal vascular pattern with aborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins
	Patchy obliteration (2)	Patchy obliteration of vascular pattern
	Obliterated (3)	Complete obliteration of vascular pattern
Bleeding	None (1)	No visible blood
	Mucosal (2)	Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope which can be washed away
	Luminal mild (3)	Some free liquid blood in the lumen
	Luminal moderate or severe (4)	Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intraluminal blood or visible oozing from a haemorrhagic mucosa

Erosions and Ulcers	None (1)	Normal mucosa, no visible erosions or ulcers
	Erosions (2)	Tiny (≤ 5mm) defects in the mucosa or a white or yellow colour with a flat edge
	Superficial ulcer (3)	Larger (> 5mm) defects in the mucosa which are discrete fibrin-covered ulcers in comparison with erosions but remain superficial
	Deep ulcer (4)	Deeper excavated defects in the mucosa with a slightly raised edge

Supplemental Table 4. Overview of Major Colon Cancer and Dysplasia Surveillance in Ulcerative Colitis Guidelines

Guideline	Major Recommendations
American Gastroenterology Association (AGA) Institute Technical Review (2010)	● All patients, regardless of the extent of disease at initial diagnosis, should undergo a screening colonoscopy a maximum of 8 years after onset of symptoms, with multiple biopsy specimens obtained throughout the entire colon, to assess the true microscopic extent of inflammation ● Patients with extensive or left-sided colitis should begin surveillance within 1 to 2 years after the initial screening endoscopy ● After 2 negative examinations (no dysplasia or cancer), further surveillance examinations should be performed every 1 to 3 years. Recent data suggest that increasing the frequency of surveillance colonoscopy to every 1 to 2 years after 20 years of disease is not needed for all patients but should be individualized according to the presence or absence of other risk factors ● Patients with a history of colorectal cancer in first-degree relatives, ongoing active endoscopic or histologic inflammation, or anatomic abnormalities such as a foreshortened colon, stricture, or multiple inflammatory pseudopolyps may benefit from more frequent surveillance examinations. ● Representative biopsy specimens from each

	anatomic section of the colon is recommended.
European Crohn's and Colitis Organisation (ECCO) European evidence based consensus for endoscopy in inflammatory bowel disease (2013)	● Screening colonoscopy should be offered at estimated 8 years after the onset of colitic symptoms to all patients to reassess disease extent ● As there is no clear evidence for surveillance intervals, individualising intervals based on risk stratification is recommended: ○ Patients with high risk features (stricture or dysplasia detected within the past 5 years, PSC, extensive colitis with severe active inflammation, or a family history of CRC in a first degree relative at less than 50 years) should have next surveillance colonoscopy scheduled for 1 year ○ Patients with intermediate risk factors should have their next surveillance colonoscopy scheduled for 2 to 3 years. Intermediate risk factors include extensive colitis with mild or moderate active inflammation, post-inflammatory polyps or a family history of colorectal cancer in a first degree relative at 50 years and above ○ Patients with neither intermediate nor high risk features should have their next surveillance colonoscopy scheduled for 5 years ○ All patients with dysplasia (within the past 5 years) irrespective of grade, should undergo annual colonoscopic surveillance ● Pan-colonic methylene blue or indigo carmine chromoendoscopy should be performed during surveillance colonoscopy, with targeted biopsies of any visible lesion. ● If appropriate expertise for chromoendoscopy is not available, random biopsies (4 every 10 cm) should be performed.

National Institute for Health and Clinical Excellence (NICE), Colonoscopic Surveillance for Prevention of Colorectal Cancer in People with Ulcerative Colitis (2011)	● Offer colonoscopic surveillance to people with inflammatory bowel disease (IBD) whose symptoms started 10 years ago and who have ulcerative colitis (but not proctitis alone) ● Offer a baseline colonoscopy with chromoscopy and targeted biopsy of any abnormal areas to determine risk of developing colorectal cancer ● Offer colonoscopic surveillance to people with IBD as defined based on their risk of developing colorectal cancer determined at the last complete colonoscopy ○ Low Risk: 5 year interval ○ Intermediate Risk: 3 year interval ○ High Risk: 1 year interval ● Risk Groups: ○ Low Risk: extensive but quiescent ulcerative colitis or left-sided ulcerative colitis (but not proctitis alone) ○ Intermediate Risk: extensive ulcerative colitis with mild active inflammation that has been confirmed endoscopically or histologically or post-inflammatory polyps or family history of colorectal cancer in a first-degree relative aged 50 years or over. ○ High Risk: extensive ulcerative colitis with moderate or severe active inflammation that has been confirmed endoscopically or histologically or primary sclerosing cholangitis (including after liver transplant) or colonic stricture in the past 5 years or any grade of dysplasia in the past 5 years or family history of colorectal cancer in a first-degree relative aged under 50 years. ● Colonoscopy with chromoscopy is the method of surveillance
SCENIC International Consensus Statement on Surveillance and Management of Dysplasia in Inflammatory Bowel Disease (2015)	● When performing surveillance with white-light colonoscopy, high definition is recommended rather than standard definition ● When performing surveillance with standard-definition colonoscopy, chromoendoscopy is recommended rather than white-light colonoscopy ● When performing surveillance with high-definition colonoscopy, chromoendoscopy is suggested rather than white-light colonoscopy ● When performing surveillance with standard-definition colonoscopy, narrow-band imaging is not suggested in place of white-light colonoscopy ● When performing surveillance with high-definition colonoscopy, narrow-band imaging is not suggested

	in place of white-light colonoscopy ● When performing surveillance with image-enhanced high-definition colonoscopy, narrow-band imaging is not suggested in place of chromoendoscopy

Supplemental Table 5. Checklist of Health Maintenance Items for Inflammatory Bowel Disease Patients*

Vaccine Preventable Illness	
	Influenza Annually for all patients. Avoid live intranasal vaccine for patients on immunosuppression
	Hepatitis B Check hepatitis B surface antigen, surface antibody and core antibody prior to initiating anti-TNF therapy. Vaccinate with non-live vaccine if non-immune.
	Pneumococcal Pneumonia If not immunosuppressed, vaccinate with PSV23. If immunosuppressed, vaccinate with pneumococcal vaccine (PCV13) followed by pneumococcal polysaccharide vaccine (PPSV23) at least 8 weeks later. Booster at 5 years.
	Varicella (chicken pox) - live vaccine Check varicella zoster virus IgG. If negative consider vaccination. Can be considered in patients on prednisone ≤20mg/day, methotrexate, 6-MP, or azathioprine but not on biologics. Can administer at least 4 weeks prior to starting biologic.
	Zoster (shingles) - live vaccine In patients 50 years or older, can be considered in patients on prednisone ≤20mg/day, methotrexate, 6-MP, or azathioprine but not on biologics. Can administer at least 4 weeks prior to starting biologic.
	MMR - live vaccine Contraindicated if any immunosuppression or planning to start immunosuppressants within 4 weeks.
	Diphtheria and Pertussis Vaccinate with Tdap if not given in last 10 years.
	HPV Vaccinate females and males ages 9 to 26 regardless of immunosuppression.

	Hepatitis A Administer to at-risk patients regardless of immunosuppression.
	Meningococcal Meningitis Administer to at-risk patients regardless of immunosuppression.
	Human Immunodeficiency Virus (HIV) Consider testing prior to starting immunosuppression. Immunosuppression not contraindicated but reports of increased risk and severity of HIV-related infections in patients on immunosuppression.[9]
Medication Related Testing	
	Mesalamines Annual renal function testing.
	Corticosteroids Assessment of bone health as indicated. Consider ophthalmology exam.
	Thiopurines TPMT, CBC, and liver function prior to initiating therapy. Regular CBC and liver function monitoring while on therapy.
	Methotrexate CBC, liver and renal function prior to initiating therapy. Regular CBC, liver and renal function monitoring while on therapy.
	Anti-TNF Tuberculosis (TB) screening prior to initiating therapy with PPD skin testing and/or QuantiFeron-TB Gold assay. Chest X-Ray (CXR) is recommended by some societies as part of initial screen.[9] CXR should also be performed if high-risk and/or indeterminate PPD or QuantiFeron-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). Check hepatitis B status prior to initiation of therapy. If surface antigen positive start prophylaxis or treatment (if PCR positive). If core antibody positive, check PCR to rule out active infection and monitor closely during treatment (every 1-3 months while on therapy).[9] CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.
	Vedolizumab CBC, liver and renal function prior to initiating therapy and periodic monitoring while on therapy.
Bone Health	
	Bone Density Assessment

	Assess bone density if the following conditions are present: 1. Steroid use >3 months; 2. Inactive disease but past chronic steroid use of at least 1 year within the past 2 years; 3. Inactive disease but maternal history of osteoporosis; 4. Inactive disease but malnourished or very thin; 5. Inactive disease but amenorrheic; 6. Post-menopausal women
	Vitamin D 25-OH Level Check at least once in all patients and supplement if deficient or insufficient.
	Calcium & Vitamin D Co-prescription of calcium and vitamin D tablets for all patients with each course of oral corticosteroids and if vitamin D deficient or insufficient.
Cancer Prevention and Health Maintenance	
	Colon Cancer If ulcerative colitis beyond the rectum or Crohn's is present in at least 1/3 of the colon, typically perform surveillance colonoscopies every 1-2 years after 8-10 years of disease, history of PSC, or history of dysplasia. However, European societies recommend considering surveillance intervals based on risk factor stratification (e.g. low risk patients can consider every 2 to 5 years for surveillance depending on guideline).[10,11]
	Cervical Cancer Annual PAP smears if immunocompromised.
	Skin Cancer Annual visual exam of skin by dermatologist if immunocompromised and recommend sun exposure precautions.
	Smoking Cessation Discuss at every visit.
	Nutritional Assessment Anemia panel (B12 in particular if history of ileal resection).

*Checklist adapted from http://cornerstoneshealth.org/checklist/checklist-for-ibd.pdf

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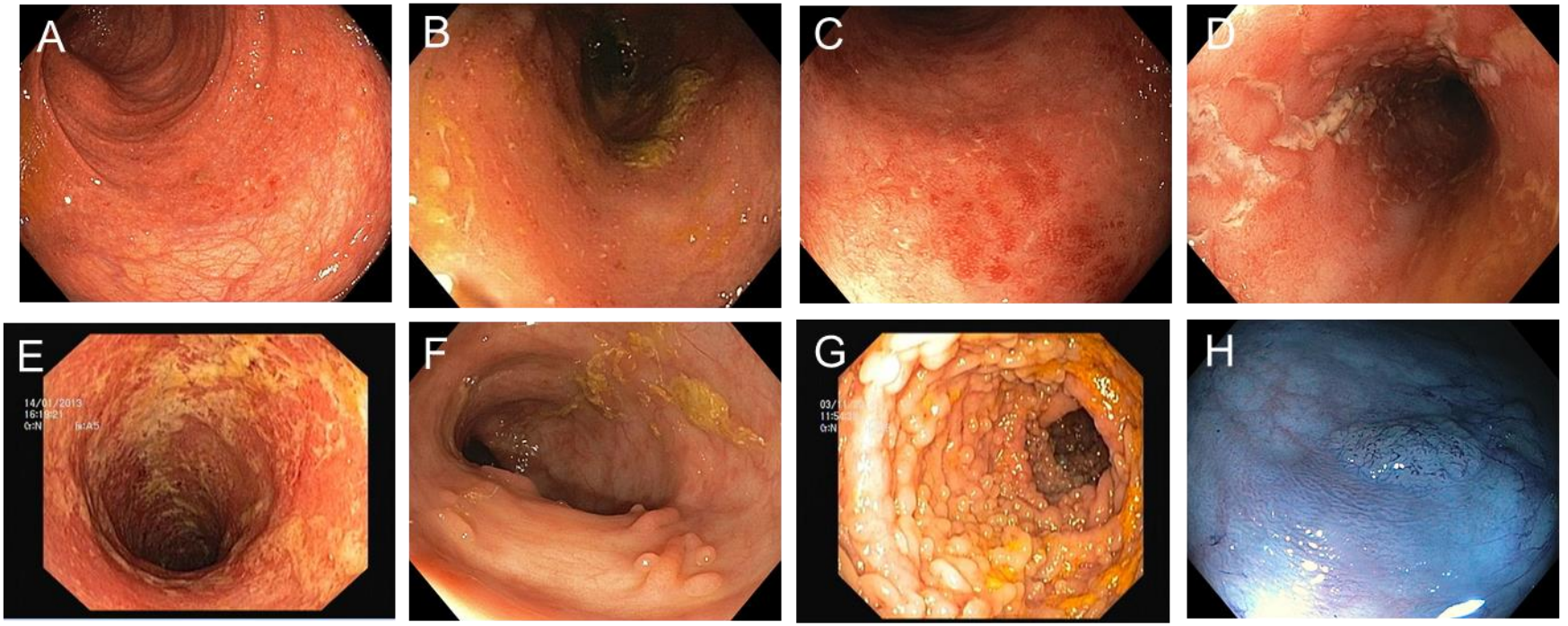
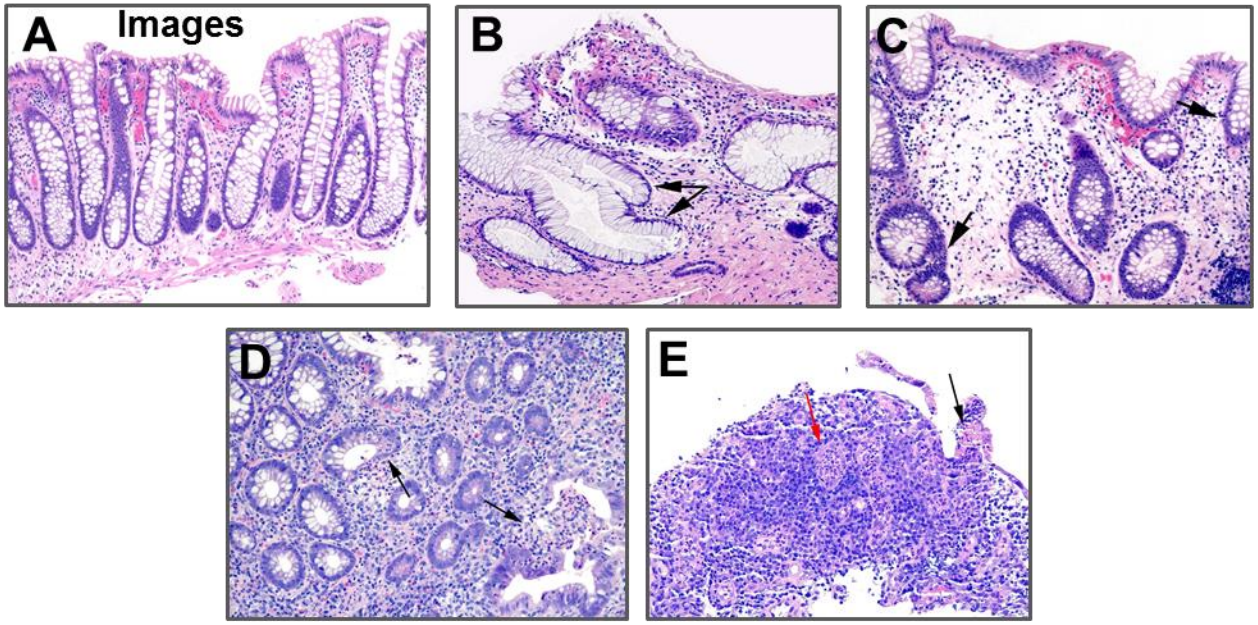
Supplemental Figure 1: Ulcerative Colitis Endoscopy Images



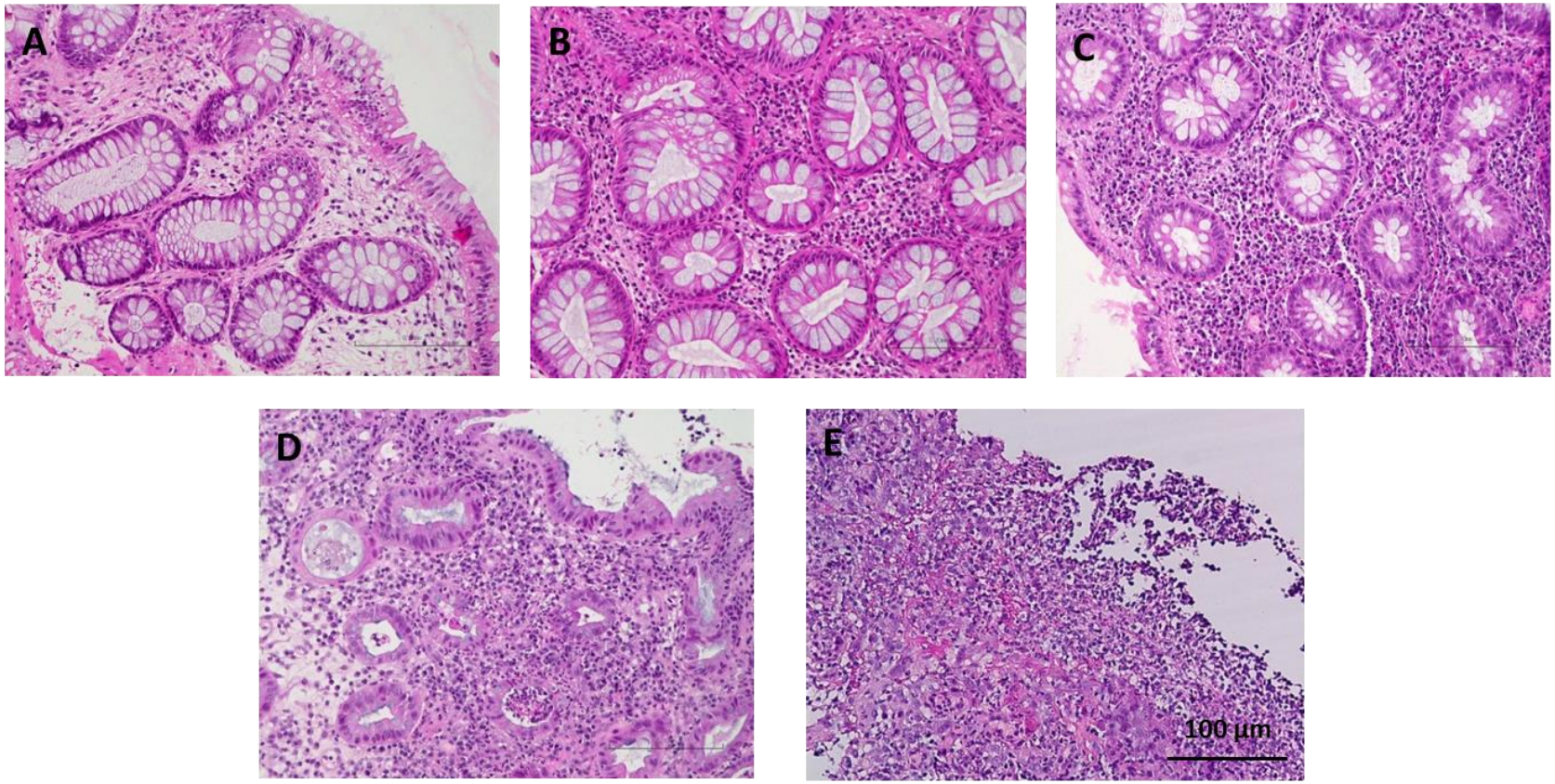
A. Mild disease with erythema and decreased vascular pattern consistent with Mayo score of 1. B. Moderate disease with loss of vascular pattern and erosions consistent with Mayo score of 2. C. Erythematous mucosa, erosions and absent vascular pattern consistent with Mayo score of 2. D. Severe disease with deep ulcerations demonstrative of Mayo score of 3. E. Severe diffuse ulcerations consistent with Mayo score of 3. F. Scattered pseudopolyps in inactive ulcerative colitis. G. Dense pseudopolyps making dysplasia surveillance difficult. H. Chromoendoscopy following application of dye spray demonstrating dysplastic lesion. *Images courtesy of Dr. Jerome Waye.*

Supplemental Figure 2: Ulcerative Colitis Histology Images



A. Normal colonic epithelium with parallel colonic crypts and absence of neutrophils. Hematoxylin and eosin stain, 100x. **B**.Inactive chronic colitis (ICC) in the sigmoid colon. The crypts are dilated and branched (arrows), a sign of chronicity, but there is no active (neutrophilic) inflammation. Hematoxylin and eosin stain, 100x. **C**.Mildly active chronic colitis (MICC) in the sigmoid colon. There is evidence of chronicity (crypt distortion and Paneth cell metaplasia) with a mild neutrophilic infiltrate in the lamina propria with neutrophils in the crypt epithelium (arrows). Hematoxylin and eosin stain, 100x. **D**. Moderately active chronic colitis (MOCC) in the sigmoid colon. Neutrophils infiltrate the lamina propria and affect most of the crypts. Arrows point to areas of cryptitis and crypt abscess. Chronicity is evidenced by the dense lymphoplasmacytic infiltrate in the lamina propria along with crypt distortion and Paneth cell metaplasia. Hematoxylin and eosin stain, 200x. **E.** Severely active colitis (SCC) in the sigmoid colon. The colonic crypts are lost, only a thin layer of epithelium remains (black arrow). The lamina propria shows full thickness lymphoplasmacytic infiltrate and neutrophils within new vessels (red arrow). Hematoxylin and eosin stain, 200x. *Images courtesy of Dr. Mabel Ko (Icahn School of Medicine at Mount Sinai, New York, NY)*

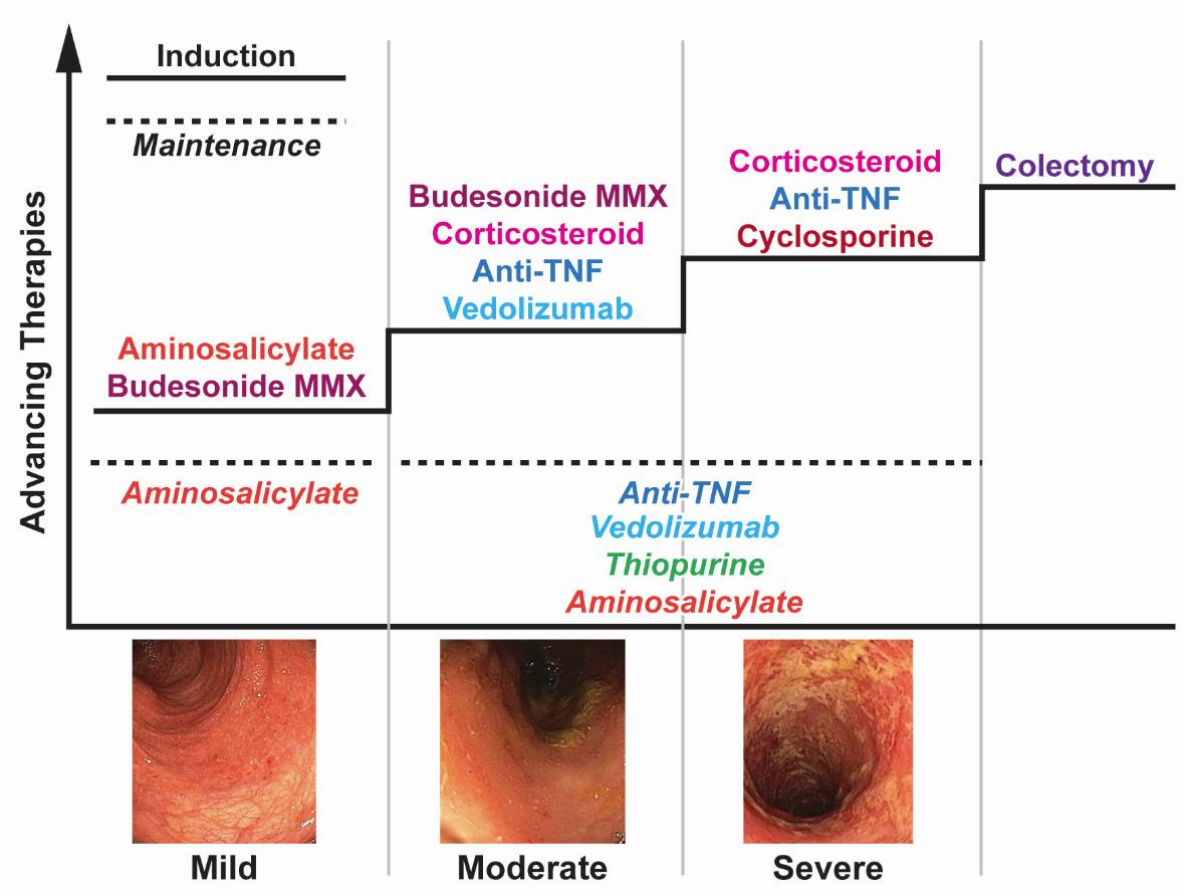
Supplementary figure 3: Nancy Index



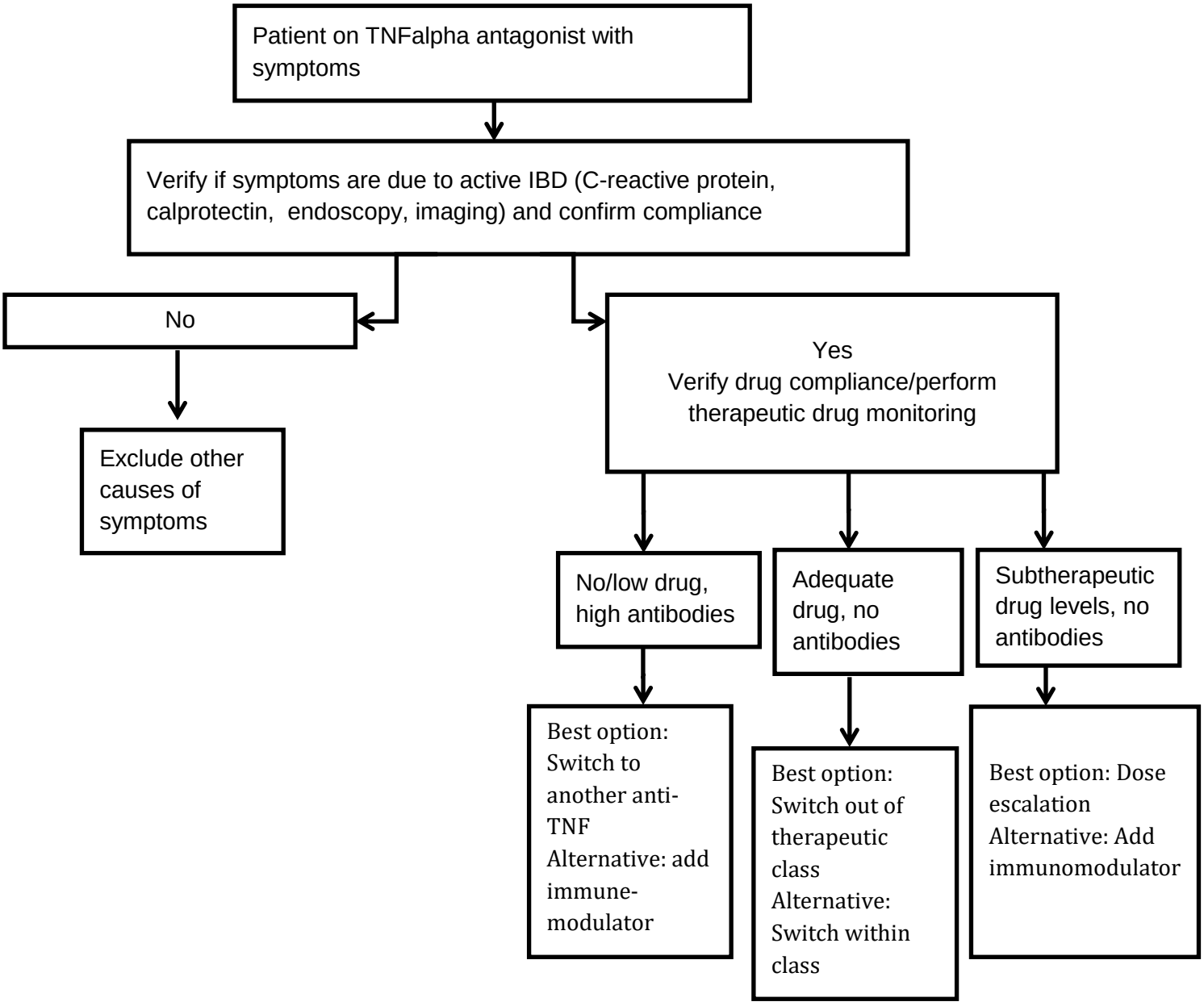
A. Grade 0 : Colonic mucosa showing mild architectural abnormalities with very mild increase of chronic inflammatory. (no histological disease) (HES x 100) **B**. Grade 1 : Colonic mucosa showing architectural abnormalities with moderate chronic inflammatory infiltrate with no acute inflammatory. (HES x 100) **C**. Grade 2 : Colonic mucosa showing few architectural abnormalities with marked chronic inflammatory infiltrate with few neutrophils (midly active disease) (HES x 200) **D**. Grade 3 : colonic mucosa showing architectural abnormalities with moderate chronic inflammatory infiltrate with numerous neutrophils (moderately active disease) (HES x 200). **E**. Grade 4 : Ulceration of mucosa with loss of colonic crypt replaced with granulation tissue (severely active disease) (HESx200)

Courtesy of Prof. Marchal-Bressenot, Reims University Hospital, France

Supplementary Figure 4



Supplementary figure 5



Adapted with permission from Roda G, Jharap B, Neeraj N, Colombel JF. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. *Clin Transl Gastroenterol* 2016; **7**: e135.